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METABOLIC AND ENDOCRINE EFFECTS OF LYSERGIC ACID DIETHYLAMIDE (LSD-25) ON MALE RATS

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SUMMARY

Male Wistar rats were injected s.c. with 500 or 750 μg./kg. of lysergic acid diethylamide (LSD-25) on alternate days for 2 weeks and received a total of eight injections, the last two being on consecutive days. Before autopsy, urinary 17-ketosteroid output, white blood cell counts, body weight, food and oxygen consumption were studied. Depending on time and dosage, the various results indicate that LSD-25 stimulates adrenal function, lowers metabolism, and inhibits thyroid and possibly gonadal function. Similarities between the effects of LSD-25 intoxication and schizophrenia are noted.

INTRODUCTION

Similarities have been reported between the psychic symptoms of lysergic acid diethylamide (LSD-25) intoxication and schizophrenia (Forrer & Goldner, 1951; Lingjaerde & Skaug, 1956). Consequently, LSD-25 has been used extensively to explore the production of reversible psychoses in non-psychotic subjects (Lingjaerde & Skaug, 1956; Sackler, Sackler, Marti-Ibanez & Sackler, 1954). Some investigators have sought to define the effects of LSD-25 on thyroid activity (Kar & Boscott, 1956; Lingjaerde & Skaug, 1956). Others have determined the effects of LSD-25 on adrenal activity by observing alterations in corticosteroid output and changes in total leukocyte and eosinophil counts (Bliss, Migeon, Branch & Samuels, 1956; Nadel, Burstein, & Hoagland, 1957; Feld, Goodman & Guido, 1958; Härkönen & Konttinen, 1958). However, reports on the effect of LSD-25 on corticosteroid output and white blood cell counts are inconsistent and often contradictory.

A previous report on the effects of LSD-25 on female albino rats (Sackler, Weltman, Russakow, Sparber & Owens, 1962) showed that LSD-25 stimulates the output of adrenocortical hormones even though it may depress metabolism and thyroidal and gonadal function. This investigation describes the effect of acute and prolonged administration of LSD-25 to male rats on the white blood cell count, body weight and the endocrine status generally.

MATERIALS AND METHODS

Forty-nine young male Wistar rats averaging 110 g. in body weight were divided into three groups. Animals in Groups A and B received a series of s.c. injections of LSD-25 (Sandoz Pharmaceuticals) (500 and 750 μg./kg. body weight, dissolved in

1 ml. of 0·9 % NaCl solution). Group C, the control rats, received the saline solution only. These doses were used in view of reports that rats and mice require more than 1000 times the effective psychomimetic dose to produce autonomic and behavioural responses in man (Nadel *et al.* 1957). In man, 50 μg. has been demonstrated to produce significant physiological and psychological alterations (Stoll, 1947; Hoagland, Rinkel & Hyde, 1955). To observe the influence of the duration of treatment, eight injections were administered during 2 weeks on alternate days, between 11.30 a.m. and 12 noon with the exception that both experimental groups were injected on the 13th and 14th day. The 2-week period and alternate days of injection were selected to avoid or minimize the development of resistance or tolerance to prolonged administration of the drug. Isbell, Fraser, Wikler & Belleville (1955) and Isbell, Belleville, Wikler & Logan (1956) showed a rapid diminution of the effect of LSD-25 in man after 7 days of treatment. Similarly Mahler & Humoller (1959) reported that rats became refractory after several injections of LSD-25 with doses ranging from 300 to 700 μg./kg.

To avoid injury by fighting during the stage of excitement after LSD-25 injections, all animals were housed singly in metal cages in air-conditioned quarters maintained at 73° F. It is recognized that acute and chronic isolation (Weltman, Sackler, Sparber & Opert, 1962) *per se* can produce behavioural, metabolic and endocrinological alterations. To minimize handling and auditory stress, all animals were subjected to equal degrees of handling; the average level of the laboratory background noise during the daylight hours was 68 decibels. Oxygen consumption and metabolic rates were determined on the 6th and 12th day approx. 24 hr. after the 3rd and 6th injections. The method, utilizing a closed system, constant pressure apparatus, was similar to that outlined by Shackell (1937).

Test and control animals were simultaneously placed in individual metabolism chambers and oxygen consumption was determined after a 30 min. acclimatization period to allow the animals to come to rest. Two 20-min. readings were taken with a 5 minute rest period between the two runs. In a few instances, when differences between the two individual measurements exceeded 10 %, a third reading was taken. The two readings or the two closest runs were then averaged and corrected to standard temperature and pressure. Oxygen consumption and metabolic rate are expressed in terms of ml./hr./kg. body weight and kcal./hr./m.^{2}. The formula of Hill & Hill (1913), based on $W^{\frac{2}{3}}$ body weight relationship was used to convert to surface area.

Urine specimens for 17-ketosteroid analysis (Rappaport, Fischl & Pinto, 1960) were collected on the 10th day for the 24 hr. period after the 5th injection. Leukocyte (Todd & Sanford, 1944) and eosinophil (Henneman, Wexler & Westenhaver, 1949) counts were obtained from tail-blood samples on the 8th day, approx. 24 hr. after the 4th injection and from a second sample taken immediately before autopsy on the 14th day.

Food consumption and body weight were determined weekly during the experimental period of 2 weeks. Within minutes after the second blood sample had been taken from the tail, all test and control animals were killed with ether and autopsies carried out. The liver, spleen, thymus, adrenals, testes, seminal vesicles, thyroids, and pituitary were dissected free from fat and were weighed to the nearest 0·1 mg. Statistical analyses were based on Student's *t*-test (Snedecor, 1949).

RESULTS

Table 1 shows body weights and food consumption during the 2-week period. The results indicate that by the second week 750 μg. LSD-25/kg. caused a significant reduction in the body weight of the test animals. The decrease produced by the smaller dose, although less pronounced, approached significance ($P = 0{\cdot}07$). Similar significant decreases were noted in the food consumption of Group B during the first and second weeks. The decreases in food consumption induced by the dose of 500 μg./kg. were not statistically significant, although the trend in this group was similar to that in Group B.

Table 1. ***Effects of LSD-25 on body weights and food consumption of male rats***

(Means ±S.E.)

Group	Dose (μg./kg.)	No. of rats	Body weight (g.)			Food consumption (g.)		
			Initial	1st week	2nd week	1st week	2nd week	Total food consumed
A	500	16	109·6 ±2·3	133·3 ±2·0	149·9 ±3·0	107·9 ±3·1	103·5 ±3·2	211·4 ±5·7
B	750	16	108·6 ±2·1	128·9 ±2·7	146·8 ±2·9	100·5 ±3·7	102·2 ±3·0	202·7 ±5·9
C	Controls	17	110·2 ±2·0	134·6 ±3·0	158·3 ±3·2	111·1 ±3·0	110·8 ±2·8	221·9 ±5·4
% diff. between A and C	—	—	−0·5	−1·0	−5·3	−2·9	−6·6	−4·7
P	—	—	0·85	0·72	0·07	0·46	0·10	0·19
% diff. between B and C	—	—	−1·5	−4·2	−7·3	−9·5	−7·8	−8·7
P	—	—	0·58	0·17	0·01	0·04	0·04	0·02
% diff. between A and B	—	—	−0·9	−3·3	−2·1	−6·9	−1·3	−4·1
P	—	—	0·75	0·20	0·47	0·14	0·77	0·30

Table 2 shows the oxygen consumption and metabolic rate approx. 24 hr. after the 3rd injection (6th day) and approx. 24 hr. after the 6th injection (12th day). Although neither oxygen consumption nor metabolic rate were significantly depressed by LSD-25 during the 1st week, pronounced effects were seen during the 2nd week. The rats injected with 500 μg./kg. showed significant decreases in oxygen consumption whether calculated as ml./hr./kg. or related to surface area. Oxygen consumption and metabolic rates in Group B animals decreased less but the differences approached significance. A reversal in the degree or range of the depressions was noted between the oxygen consumption readings on the 6th and 12th day of the experiment. In the first period, the larger decrease was induced by the dose of 750 μg./kg. Decreases were also noted in the oxygen consumption measurements of all test and control groups on the 12th day as opposed to their values on the 6th day (Group A *v.* A; B *v.* B; C *v.* C). Although habituation and/or environmental factors might account for part of these decreases, habituation caused by repeated exposure to the

metabolism chamber could not by itself account for the significant and marked decreases in the metabolic rates of Group A and B as compared with those in the control group on the 12th day.

Table 3 presents the leukocyte and eosinophil counts obtained approx. 24 hr. after the 4th and 8th injections (8th and 14th days), and the total 17-ketosteroid values in urines collected in the 24 hr. period after the fifth injection (10th day). The larger dose produced significant decreases in the leukocyte and eosinophil counts at both

Table 2. *Effect of LSD-25 on the oxygen consumption and metabolic rate of male rats*

(Means ± S.E.)

Group	Dose (μg./kg.)	No. of rats	24 hr. after 3rd injection (6th day)		24 hr. after 6th injection (12th day)	
			Oxygen consumption (ml./hr./kg.)	Metabolic rate (kcal./hr./m.²)	Oxygen consumption (ml./hr./kg.)	Metabolic rate (kcal./hr./m.²)
A	500	16	1493·4 ± 58·9	40·02 ± 1·70	1308·3 ± 31·0	36·14 ± 0·96
B	750	16	1464·2 ± 59·2	38·70 ± 1·78	1373·6 ± 46·6	37·60 ± 1·44
C	Controls	17	1558·1 ± 59·6	41·70 ± 1·73	1463·3 ± 41·0	40·75 ± 1·32
% diff. between A and C	—	—	−4·2	−4·0	−10·6	−11·3
P	—	—	0·45	0·49	< 0·01	< 0·01
% diff. between B and C	—	—	−6·0	−7·2	−6·1	−7·7
P	—	—	0·28	0·24	0·16	0·12
% diff. between A and B	—	—	−2·0	−3·3	+5·0	+4·0
P	—	—	0·73	0·60	0·26	0·41

periods. Significant but smaller decreases in leukocyte counts were also produced by 500 μg./kg. In contrast, the decreases in the eosinophil count bordered on significance after the 4th injection ($P = 0{\cdot}06$) but were not significant on the 14th day. The differences between the degree of fall in the eosinophil counts in Groups A and B may be due to dosage effects or may well reflect less reliability in the eosinophil counting procedure (Bibile, 1953).

The values for urinary 17-ketosteroids obtained during the 24 hr. after the 5th injection (10th day) indicated a significant increase (39·7 %) in the rats that received the higher dose. The increase of 25·1 % observed in the animals of Group A approached statistical significance ($P = 0{\cdot}10$). The order of magnitude and degree of alteration of the 17-ketosteroid levels on the 10th day, coincided with the degree of change in the leukocyte and eosinophil counts on the 8th day.

Table 4 shows the organ weights of the test and control animals killed after 2 weeks. The smaller dose of LSD-25 (500 μg./kg.) produced marked decreases in the final

Table 3. *Effect of LSD-25 on white blood cell (WBC) and eosinophil (EO) counts and urinary 17-ketosteroid (17-KS) output of male rats*

(Means ± S.E.)

Group	Dose (μg./kg.)	24 hr. after 4th injection (8th day)			24 hr. after 8th injection (14th day)		24 hr. values after 5th injection* (10th day)	
		No. of rats	WBC/mm.³	EO/mm.³	WBC/mm.³	EO/mm.³	No. of Rats	17-KS (μg./day)
A	500	15	11031·7 ±713·0	52·3 ±8·1	11195·0 ±323·6	52·7 ±7·1	15	39·4 ±3·6
B	750	16	9757·8 ±493·3	40·3 ±4·3	10167·2 ±252·9	45·0 ±4·9	12	44·0 ±4·1
C	Controls	17	13604·4 ±598·1	82·6 ±12·5	13385·3 ±485·8	63·5 ±6·0	13	31·5 ±2·9
% diff. between A and C	—	—	−18·9	−36·7	−16·4	−17·0	—	+25·1
P	—	—	< 0·01	0·06	< 0·001	0·26	—	0·10
% diff. between B and C	—	—	−28·3	−51·2	−24·0	−29·1	—	+39·7
P	—	—	< 0·001	< 0·01	< 0·001	0·02	—	0·02
% diff. between A and B	—	—	−11·5	−22·9	−9·2	−14·6	—	+11·7
P	—	—	0·16	0·19	0·02	0·38	—	0·41

* Urine volume collected for a 24-hr. period following 5th injection.

Table 4. *Effect of LSD-25 on absolute organ weights of male rats*

(Means ± S.E.)

Group	Dose (μg./kg.)	No. of rats	Final body wt. (g.)	Liver (g.)	Spleen (mg.)	Thymus (mg.)	Adrenals (mg.)	Testes (g.)	Seminal vesicles (mg.)	Thyroids (mg.)	Pituitary (mg.)
A	500	16	149·9 ± 3·0	7·0570 ± 0·2404	303·5 ± 13·7	214·0 ± 11·8	25·3 ± 1·1	1·8611 ± 0·0397	74·9 ± 7·6	11·9 ± 0·4	5·7 ± 0·2
B	750	16	146·8 ± 2·9	6·7166 ± 0·2047	290·8 ± 18·2	225·8 ± 10·3	22·3 ± 0·9	1·8703 ± 0·0544	77·0 ± 7·4	12·0 ± 0·6	5·4 ± 0·2
C	Controls	17	158·3 ± 3·2	7·3712 ± 0·2484	380·2 ± 15·3	234·4 ± 10·8	21·1 ± 0·6	1·8995 ± 0·0899	94·0 ± 8·3	13·2 ± 0·4	5·6 ± 0·2
% diff. between A and C	—	—	−5·3	−4·3	−20·2	−8·7	+19·9	−2·0	−20·3	−9·8	+1·8
P	—	—	0·07	0·37	< 0·001	0·21	< 0·01	0·70	0·10	0·03	0·75
% diff. between B and C	—	—	−7·3	−8·9	−23·5	−3·7	+5·7	−1·5	−18·1	−9·1	−3·6
P	—	—	0·01	0·05	< 0·001	0·57	0·29	0·79	0·14	0·10	0·54
% diff. between A and B	—	—	−2·1	−4·8	−4·2	+5·5	+11·9	+0·5	+2·8	+0·8	−5·3
P	—	—	0·47	0·29	0·58	0·35	0·05	0·89	0·84	0·88	0·28

body weights ($P = 0{\cdot}07$) and significant decreases in the weights of the spleen and thyroids; the decrease in the weight of the seminal vesicles approached significance ($P = 0{\cdot}10$). The weight of the adrenals increased significantly ($+19{\cdot}9\,\%$). Similarly, the rats in Group B showed significant decreases in the final body weight and spleen and liver weights; decreases in thyroid and seminal vesicle weights approached significance. Although the absolute weight of the adrenals was not significantly altered, significant increases could be demonstrated with doses of both 500 and 750 μg./kg. when adrenal weight was related to body weight. Comparison of the effects of the two doses indicated that decreases in the final body weights, liver and splenic weights were greater in Group B. In contrast, the changes in the weights of the adrenals and the thymus were relatively more pronounced in Group A.

Impressions of behavioural characteristics and alterations produced by acute and prolonged administration of LSD-25 indicated that generally the test animals appeared to display a greater initial activity within minutes after the injections. Subsequently, the treated rats became considerably quieter, more passive and would retreat to the farthest corner of the cage. Prolonged administration seemed to create additional states of confusion in the general locomotor activity of the rats with suggestions of increased withdrawal symptoms. However, while some test rats tended to resist removal from the cage and resisted injections by attempting to bite, other test rats were considerably quieter and more passive than the controls in their reaction to handling.

DISCUSSION

The results of the present investigation of the effects of LSD-25 in male animals agree with those of Sackler *et al.* (1962) on female Wistar rats in that they indicate an increased output of adrenocorticosteroids, reduced thyroid function, and a lowered rate of metabolism as well as, possibly, a decrease in the gonadal activity of the male rats investigated. Furthermore, greater susceptibility of the males to LSD-25 is indicated by a more pronounced fall in body weight than in females.

The rise in the excretion of urinary 17-ketosteroids is in accord with reports that LSD-25 increases 17-ketosteroid output in man (Vojtechovsky, Gros, Vitek, Rysanek & Bultasova, 1960). The changes in white blood cell counts are likewise in agreement with reports in man that administration of LSD-25 causes lymphopenia (Belsanti, 1952) and eosinopenia (Feld *et al.* 1958). The findings are of further interest because they not only indicate marked or significant increases in 17-ketosteroid levels within the first 24 hr. after an injection, but also significant and persistent decreases in white blood cell counts which were still evident 24 hr. after the 4th and 8th injections. These results consequently support the observation of significant increases in the relative adrenal weights of both groups treated with LSD-25 and the significant increases noted in the absolute adrenal weights of animals in Group A.

Evidence for reduced thyroid function in the test groups is based on the significant decreases in oxygen consumption, metabolic rate, and changes in thyroid weight in Group A and the similar although less marked decreases in Group B. These results confirm reports of Kar & Boscott (1956) and Lingjaerde & Skaug (1956) of a decreased uptake of ^{131}I and ^{32}P by the thyroids of rats treated with LSD-25 and confirm the observations of Savage (1962) of reduced food intake and body weight losses in

human subjects given LSD-25. This shift may be due to the catabolic effects caused by increased release of adrenocorticosteroids as well as to the decrease in food consumption and other unknown factors. Additional evidence for a disturbed metabolism is provided by the decreases observed in the absolute liver weights (moderate in Group A and significant in Group B). Analyses of the ratio weight gain:food consumed, showed that the utilization of food was significantly depressed in both test groups during the 2nd week of treatment. The rats in Group A displayed the greatest reduction in food utilization (−26·8%).

In evaluating the physiological and biological effects of LSD-25 on adrenal, thyroid, gonad and lymphoid organ interrelationships, it becomes apparent that the various endocrine and thymic changes resemble those typically and characteristically produced by non-specific stress agents (Selye, 1936; Selye & Fortier, 1950). The population density studies with male mice of Christian (1955, 1956) have similarly shown marked gains in adrenal weight as well as a decline in body, thymic, gonadal and accessory reproductive organ weights of mice exposed to the stress of overcrowding. Yet, to characterize the action of LSD-25 on the metabolism and endocrine system of the test rats solely as a non-specific stress appears to be an over-simplification. The resemblance of the psychic symptoms caused by minute doses of LSD-25 to schizophrenia merits further reflexion. Malitz, Esecover, Wilkens & Hoch (1960) believe that hallucinogenic agents such as LSD-25 act in two ways: (1) like a toxic agent producing autonomic disturbances and distortions of visual perception, and (2) as non-specific psychic stress. Condrau (1949) has advanced the concept that psychoses may be the result of endogenously-produced substances similar to LSD-25. Rinkel, Hyde & Solomon, (1955) postulated that LSD-25 may interfere with adrenaline metabolism yielding noxious and deleterious metabolites. Lingjaerde & Skaug (1956) have also claimed that the disturbances in carbohydrate metabolism found in schizophrenics may be similar to those produced by LSD-25.

Although individual behaviour and performance responses were not observed in depth or related to changes in individual metabolism and endocrine function, such studies are needed. Various investigators have studied temporary and transient effects of LSD-25 on the climbing performance of rats (Mahler & Humoller, 1959), on the hyperexcitability, aggressiveness and muscle co-ordination of mice (Haley, 1957) and on shock-avoidance responses of rats (Jarrard, 1963). Studies of hallucinogenic effects on aggressiveness, timidity and emotionality of laboratory animals correlated with metabolic and endocrine organ alterations may be interesting.

Although it is dangerous to relate behaviour and endocrine alterations in laboratory animals to schizophrenia, the present study shows a parallel to certain toxic responses to LSD-25 in acute and chronic schizophrenia which may go beyond mere psychomimetic similarities. In general, the pattern of the present findings caused by administration of LSD-25 to male rats parallels the endocrine status observed in schizophrenics. An increased output of adrenocorticosteroid has been reported in schizophrenic patients (Sackler, Sackler, Sackler & van Ophuijsen, 1950; Bliss *et al.* 1956; Altschule, 1957). Furthermore, increased adrenocortical activity with or without thyroid malfunction (Sackler, Sackler, Marti-Ibanez & Sackler, 1956), hypogonadism (Sackler, Sackler, Co Tui, Marti-Ibanez, La Burt & Sackler, 1952) and/or thymic hypofunction have been associated with this psychiatric

disorder. The endocrinological pattern has been reproduced with LSD-25. Thus, the present findings support the concept that increased adrenocortical function together with relative or absolute hypothyroidism and/or hypogonadism may be associated with etiological and pathogenetic factors in some of the schizophrenias (Sackler, Sackler, Sackler & van Ophuijsen, 1952; Sackler *et al.* 1954).

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